ORIGINAL ARTICLE

FACTORS ASSOCIATED WITH UNSUCCESSFUL TREATMENT OUTCOME OF PULMONARY TUBERCULOSIS IN KOTA BHARU, KELANTAN

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ABSTRACT

Treating tuberculosis (TB) remains a public health challenge in many developing countries. Treatment success rate in Malaysia is on declining pattern from 78% in 2000 to 48% in 2006. This study will determine factors associated with unsuccessful treatment among pulmonary TB patients. A retrospective cohort study was conducted on notified and treated pulmonary TB cases in Kota Bharu district Kelantan between January 2006 and December 2007. To identify the associated factors, univariate comparison and multiple logistic regressions were performed. Among the 765 patients identified, 472 (61.7%) cases fulfilled the criteria and were analyzed. There were 316 males and 156 females and their mean (SD) age was 45 (17.9) years. In univariable analysis, age, gender, educational level, employment status, family incomes as well as co-existence of extra-pulmonary TB, smoking, co-morbid disease (diabetes mellitus), HIV status, sputum cultures, chest X-ray findings and duration of delay for diagnosis were all found to have significant relationship with unsuccessful pulmonary TB treatment outcome. After adjusted for the confounders, the significant predictors for unsuccessful tuberculosis treatment were age (Adj. OR 1.09; 95% CI: 1.03-1.15), HIV positive (Adj. OR 23.04; 95% CI: 3.01-176.22) and advanced chest X-ray findings (Adj. OR 6.51; 95% CI: 1.50-28.23). A large proportion of unsuccessfully treated cases could be identified at entry by screening for age, chest X-rays and HIV status and specially targeted measures could be taken. The use of directly observed treatment short-course (DOTS) should be given more focus and priority among this high risk group of patients.

Key words: Pulmonary tuberculosis, MDR TB, HIV, treatment outcome

INTRODUCTION

Tuberculosis (TB) remains a common and deadly disease in the world and has an enormous economic impact on many countries[1]. Based on the existing surveillance and survey data, the World Health Organization (WHO) estimates that 9.27 million new cases of TB occurred in 2007 (139 per 100 000 population). Of these, Asia (the South-East Asia and Western Pacific regions) accounts for 55% of global cases. Globally, the total number of cases is still increasing in absolute terms as a result of population growth. In 2007 alone, there were 1.32 million deaths from TB in HIV negative people with an additional 0.46 million TB deaths in HIV-positive people. Collectively, these statistics show that TB remains a major global health problem[2].

The South-East Asia region, with an estimated of 4.88 million prevalent cases and an annual incidence of 3.17 million TB cases, carries one-third of the global burden of TB[3]. In Malaysia for the year 2004, 15,429 new cases of TB were reported. Majority of the cases were in the economically productive age group (15-54 years old)[4]. There were 1,263 cases of HIV and TB co-infections notified for the same year. The total number of deaths due to TB reported was 1,245. This makes TB the single most important killer amongst notifiable infectious diseases in Malaysia[5]. Besides being a deadly disease, TB is also a costly disease which can give a great economical impact to the country. The cost of anti-TB drugs constituted the highest proportion of the cost to the public services (31.7%) while the cost to the patient constitutes 80% of the total costs of the treatment[6].

One of the priorities in the control of tuberculosis is to cure patients with the disease, given that the most effective way to prevent transmission and avoid the appearance of drug-resistant strains is to detect cases of tuberculosis early and treat them appropriately. WHO has set a goal of curing at least 85% of infectious patients as part of the program to control tuberculosis. WHO has defined the treatment success as the sum of patients who are cured and those who have completed treatment[7]. According to WHO database, treatment success

rate in Malaysia is on declining pattern ranging from 78% in 2000 to 48% in 2006[8]. Based on this fact, it appears that there is still room for improvement, particularly in terms of achieving a better cure rate.

Completing TB treatment is challenging for patients because treatment takes a minimum of 6 months, may require frequent clinic visits for medication refills and monitoring and may cause unpleasant side effects. To achieve targeted cure rate, the WHO recommends a directly observed treatment, short-course (DOTS) strategy, in which surveillance of the treatment outcome makes an essential contribution to the assessment of the effectiveness of control programs. This strategy has shown improvement in the cure rate in many countries. However, in Malaysia, TB treatment success rate had declined from 70% in 2005 to 48% in 2006, despite having good 100% DOTS (Directly Observed Treatment, short course) coverage from 2000 to 2007[8]. In the state of Kelantan alone, treatment success rate in 2007 was only 66.6%.

There are studies done to identify the associated factors that can influence the treatment outcomes for tuberculosis treatment elsewhere. Among associated factors that were highlighted in the literature were demographic factors[1], co-morbid diseases such as diabetes and HIV[1], chest radiograph findings[9,10], history of previous TB treatment[1,9], sputum cultures[11] and drug susceptibility testing for *Mycobacteria*[1], multi-drug resistance status[1,12] as well as smoking status[13]. This study will enable us to look for specific reasons for unsuccessful treatment outcome in order to improve the treatment system.

MATERIALS AND METHOD

Study design

A retrospective cohort study was conducted on notified and treated pulmonary tuberculosis cases in Kota Bharu district in Kelantan between 2006 and 2007. Secondary data used in this study were obtained from Malaysian Ministry of Health online database e-Notifikasi, Tuberculosis Information System (TBIS) 101A registration book and relevant TBIS forms that were submitted to Kota Bharu District Health Office. TBIS is a web-based application used by Ministry of Health Malaysia to record activities of notification, registration, investigation and treatment of TB diseases.

Operational definitions

Education level was categorized into two categories which were "Low" if the respondents had underwent up to primary school level and "High" if they underwent at least secondary school level. Meanwhile, family income was defined as total household income earned by the respondents. Based on Clinical Practice Guidelines for the Control and Management of Tuberculosis, TB cases were categorized into:

- New TB case: for respondent who was newly diagnosed for TB and never receives TB treatment before or had received TB treatment less than 4 weeks in the past or claimed that he had received TB treatment with no previous registration proof.
- Relapse TB case: for TB case that has completed TB treatment that was confirmed cured or completed treatment but reactivated with positive sputum smear or by bacteriological, histological or radiological examination.
- Treatment after interruption: for TB case that had restarted treatment after previous treatment interruption.
- Treatment after failure: for TB case that has restarted treatment after previous treatment failure.

For tuberculin test, it was considered "Positive" if the skin induration was equal or more than 10mm and "Negative" if the induration less than 10mm or absent at all. BCG scar was considered "Present" if the scar was equal or more than 2 mm including keloid and "Absent" if less than that. For chest X-ray finding, it was considered "Minimal" when there was either no lesion or only slight lesions without demonstrable cavitations confined to a small part of one or both lungs. The total extent of the lesions should not exceed the volume of lung on one side which lies above the second chondrosternal junction and the spine of the fourth or the body of the fifth thoracic vertebra [5]. Other than that finding, it was categorized as "Advanced" chest X-ray finding.

In the present study, duration of delay for diagnosis in diagnosis was defined as the duration (in days) between onset of TB symptoms and commencement of anti-TB treatment. Meanwhile, ttreatment outcome was categorized as either "Successful" or "Unsuccessful". It was "successful" when the respondents have either successfully cured (if they were smear-negative at or at least one month prior to the completion of treatment and on at least one

previous occasion) or completed treatment (when smear negative TB patient has completed treatment with no proof of cure). On the other hand, it was "unsuccessful" when they have either treatment failure (it was either for smear positive TB patients who while on treatment, remained or become smear positive again five months or later after commencing treatment or for smear negative TB patients who become smear positive after two months commencing treatment) or died due to TB during the treatment.

Statistical analysis

Data entry and analysis were done using SPSS version 12.0. All continuous variables were described using mean (SD) whereas for categorical data as frequency (%). Treatment success rate was calculated as the percentage of those who were categorized as "Successful" outcome and all study respondents as the denominator. Both univariable and multivariable analysis using simple logistic regression and multiple logistic regression analysis respectively were performed to determine the associated factors and significant predictors for the Pulmonary TB treatment outcomes. All variables with *p*-value of <0.25 in simple logistic regression were included in multiple logistic regression during variable selection process. Variables with *p*-value ≥0.25 required additional evidence of importance, for instance known clinical importance, before inclusion in the multivariable analysis.

Two methods of variable selection were used which were forward and backward stepwise variable selection methods to obtain preliminary model and the highest number of variables was included in the further analyses. However, if the selected variable *p*-value was >0.05, the respective variable was removed manually and excluded from the model. The removal of that variable was based on the decision of *p*-value from the Wald statistics. With all significant and important variables, the preliminary main-effect model was obtained. In the analysis, we checked for multicolinearity and interaction term problems. Multicolinearity problem was checked using correlation matrix and standard error. Then, preliminary final model was obtained.

To assess the fitness of model, Hosmer Lemeshow goodness of fit test, classification table and ROC curve were used. The final model was determined by enter method. The adjusted odds ratio was estimated with 95% confidence interval. Findings were presented with crude and adjusted OR, 95% CI and *p*-value. The level of significant for all analysis was set at 0.05.

Ethical issues

Confidentiality was well kept during this study using anonymous technique, in which only researcher was assessable to the name of patients. This study was approved by the Research Ethics Committee (Human), Universiti Sains Malaysia on 29th September 2009 and Medical Research Ethics Committee (MREC), Malaysian Ministry of Health on 11th November 2009.

RESULTS

During the two-year period (2006-2007), there were 765 pulmonary tuberculosis (TB) cases notified in Kota Bharu District Health Office. Of these, 472 (61.7%) cases fulfilled the criteria and were included in the analysis. The mortality rate for pulmonary TB patients was 6.8 per 10^5 populations. There was only one case (0.2%) of treatment failure identified. Treatment outcomes of all patients were classified into two groups which were successful treatment outcome (cure/completed treatment) (n = 439; 93.0%) and unsuccessful treatment outcome (treatment failure / death) (n = 33; 7.0%).

There were 316 males and 156 females and their mean (SD) age was 45(17.9) years. The majority of patients were Malays (95.1%), Malaysian citizen (98.7%), married (58.3%) and living in urban area (59.3%). These patients mostly (79.4%) have high average educational level (secondary school and above), lower income group (71.2%) with overall rate of unemployment was 45.6%. Majority were newly diagnosed pulmonary TB (n=425; 90.0%). About 40% of patients were known smokers, 12.1% (n = 57) were HIV positive and about a quarter of patients (n=116) were diabetic (Table 1).

Table 1. Socio-demographic and clinical characteristics of 472 patients* with pulmonary TB reported in Kota Bharu, 2006 – 2007

Characteristics	n	%
Gender (n = 472)		
Male	316	66.9
Female	156	33.1
Race (n = 472)		
Malay	449	95.1
Non-Malay	23	4.9
Citizenship (n = 472)		
Malaysian	466	98.7
Non-Malaysian	6	1.3
Marital status (n = 441)		
Single or divorcee	166	37.6
Married	275	62.4
Education level (n = 415)		
Low	98	23.6
High	317	76.4
Employment (n = 443)		
Employed	228	51.5
Unemployed	215	48.5
Family income (n = 415)		
< RM 1000	336	81.0
≥ RM 1000	79	19.0
Case categories (n = 472)		
New case	425	90.0
Relapse case	36	7.6
Treatment after interruption	11	2.4
Smoking (n = 450)		
Yes	195	43.3
No	255	56.7
HIV status (n = 472)		
Positive	57	12.1
Negative	415	87.9
Diabetes mellitus (n = 456)		
Yes	116	25.4
No	340	74.6

**Sample sizes may differ secondary to missing values*

Table 2 shows detailed causes of death among the respondents. Causes of death were documented in only 28 (87.5%) out of 32 deaths. The causes were categorized into two major groups which are HIV positive and non HIV cases. Majority of PTB death cases were among the non HIV patients (62.5%). PTB death cases with HIV positive accounts for 25% of all death. PTB alone is the majority cause of death in both HIV (15.6%) and non HIV (37.5%).

Table 2. Detailed causes of death among 32 pulmonary TB patients* reported in *Kota Bharu*, 2006 – 2007

Causes of death	n	%
HIV positive		
PTB with complications	10	31.3
PTB with chronic liver disease	1	3.1
Non HIV		
PTB with complications	14	43.7
Atypical PTB	1	3.1
PTB with COAD	2	6.3
Missing data	4	12.5

**Sample sizes may differ secondary to missing values*

In univariable analysis, age, gender, lower educational level, unemployed and lower family income were found to have significant relationship with unsuccessful pulmonary TB treatment outcome. By clinical characteristics, case categories (in term of treatment after interruption as compared to new case), smoker and positive HIV showed significant association with unsuccessful pulmonary TB treatment outcome. Negative tuberculin test, positive sputum cultures, advanced chest X-ray findings and longer duration of delay for diagnosis were significantly associated with unsuccessful pulmonary tuberculosis treatment outcome (Table3).

Table 3. Associated factors for unsuccessful treatment outcome (treatment failure or death) among pulmonary TB patients in Kota Bharu, Kelantan from 2006 - 2007 using simple logistic regression analysis

Variables	Crude OR (95% CI)	*p*-value
Socio-demographic characteristics:		
Age (n = 472)	1.02 (1.00 – 1.04)	0.060
Male (n = 472)	0.34 (0.13 – 0.90)	0.030*
Malays (n= 472)	0.59 (0.08 – 4.53)	0.614
Married (n = 441)	1.42 (0.69 – 2.90)	0.337
Low education (n = 415)	3.44 (1.67 –7.11)	0.001*
Unemployed (n = 443)	2.61 (1.21 – 5.63)	0.014*
Lower family income (n = 415)	8.21 (1.11 – 61.02)	0.040*
Case categories:		
New case (n = 425)	1.00	-
Relapse case (n = 36)	2.70 (0.96 – 7.55)	0.059
Treatment after interruption (n = 11)	9.55 (2.61 – 34.88)	0.001*
Clinical characteristics:		
Extra-pulmonary TB (n = 472)	2.34 (0.65 – 8.39)	0.192
Abscence BCG scar (n = 472)	1.29 (0.58 – 2.86)	0.534
Smoker (n = 450)	6.67 (2.70 – 16.50)	<0.01*
HIV positive (n = 472)	5.84 (2.72 – 12.54)	<0.01*
Diabetic (n = 456)	0.78 (0.33 – 1.84)	0.564
Case management characteristics:		
Negative tuberculin test (n = 167)	2.50 (0.85 – 7.39)	0.098
Positive sputum cultures (n = 417)	2.51 (1.08 – 5.84)	0.032*
Positive sputum smears (n = 472)	1.26 (0.51 – 3.14)	0.620
Advanced chest X-ray findings (n = 468)	2.15 (1.05 – 4.38)	0.036*
Longer duration of *delay for diagnosis*(n = 472)	1.00 (1.00 – 1.00)	0.076

***** *Significant at p<0.05*

In multiple logistic regression analysis, the significant predictors for unsuccessful pulmonary TB treatment were age, positive HIV and advanced chest X-ray findings. Table 4 shows the final model of the analysis. The model can be interpreted as follows:

- a pulmonary TB patient with one year increase in age has 1.09 times the odds to have unsuccessful treatment outcome (95% CI: 1.03 - 1.15, $p = 0.001$).
- a HIV positive pulmonary TB patient has about 23 times the odds to have unsuccessful treatment outcome as compared to non HIV patient. (95% CI: 3.01 - 176.22, $p = 0.003$).
- a patient with advanced chest X-ray finding has 6.5 times the chance to have unsuccessful treatment outcome as compared to those with minimal chest X-ray finding (95% CI: 1.50 - 28.23, $p = 0.012$).

Table 4. Significant associated factors for unsuccessful treatment outcome (treatment failure or death) among pulmonary TB patients in Kota Kelantan using multiple logistic regression analysis

Variables	OR (95% CI)	*p-value*	Wald	Adj. OR (95% CI)	*p-value*
Age (n = 472)	1.02 (1.00 – 1.04)	0.060	4.20	1.09 (1.03-1.15)	0.001
HIV positive (n=472)	5.84 (2.72 –12.54)	<0.001	9.14	23.04 (3.01-176.22)	0.003
Advanced chest X-ray findings (n=468)	2.15 (1.05 – 4.38)	0.036	6.25	6.51 (1.50-28.23)	0.012

Model fitness was checked with Hosmer and Lemeshow test (p-value 0.37), area under the Receiver Operating Characteristics curve was 0.78 and the overall percentage correct was 92.9%. There were no multicollinearity problem and interaction noted.

DISCUSSION

Treatment success rate in the current study was good and it exceeded the WHO international target of 85%. The mortality rate of pulmonary tuberculosis patients in Kota Bharu was 6.8 per 100 000 populations. The rate is still considered to be high as the desirable tuberculosis mortality rate by WHO was <3 per 100 000 populations[14]. The results also showed that a quarter of tuberculosis death cases were among HIV positive patients.

Seventy-five percent of TB cases in developing countries are among the economically productive age group. In Malaysia, the incidence of tuberculosis in 2000 was highest among the 20-54 years age group[15] which is about similar to this study in which the mean age was 45 years. Age of patients with successful treatment outcome group [mean (SD) = 45 (17.9)] were significantly younger than the unsuccessful treatment outcome group [mean (SD) = 51 (18.9)].

Concerning gender, about one third of tuberculosis cases in the present study were female. While there have been steep increases in women engaging in risk behaviours such as alcohol, substance and tobacco abuse, such behaviours are still predominantly seen in men. The women could also have been infected tuberculosis from their spouses. Another contributing factor is the high-TB incidence in prisons, whose populations consist mostly of men. In the current study, gender was not a significant predictor for the treatment outcome. In contrast, Vinod and Anna (1999) found that female was a predictor for unsuccessful TB outcome due to limited access to health care facilities causing delayed in diagnosis and treatment as well as more social stigma for women with TB[16].

A study in a developing country (Estonia) suggested that the main risk factors for TB were poverty and current smoking[17]. This is consistent with the current study which found that among respondents, 71% had lower family income (<RM 1000) and 41% were smoking. In contrast with the study which found that unmarried and poor education as the main risk factors for TB, the current study found that 35% of the respondents were unmarried or divorcee and 21% had low education level.

Majority of the respondents were newly diagnosed cases and relatively had mild disease as evidenced by minimal lesion on chest X-rays findings in more than half of them. The study found that TB case category (whether relapse or interrupted treatment as compared to new case) was not significantly associated with the treatment outcomes. This could be due to most of the respondents (90%) were new cases as compared to other categories. In contrast, de Albuquerque et al (2007) found that history of prior TB treatment was significantly associated with unsuccessful treatment outcomes[18]. Similarly, Anunnatsiri et al (2005) also found that

history of previous TB treatment was associated with treatment failure and death[1].

The coexistence of extra-pulmonary tuberculosis occurred in minority of cases. Even though other studies showed that coexistence of extra pulmonary tuberculosis as a significant predictor for treatment outcome, our study shows a different result. Coexistence of extra-pulmonary tuberculosis was not a significant predictor for treatment outcome in our study probably because of a very low proportion (about 4%) among them had extra pulmonary tuberculosis.

In the study, about 25% of the patients have diabetes. Even though diabetes mellitus is a significant risk factor for tuberculosis[19], our study shows that it does not significantly associated with the treatment outcome. Results in the previous studies also vary regarding the association of diabetes mellitus and tuberculosis treatment outcomes. A study in Iran showed that diabetes was a significant risk for tuberculosis death[20]. On the other hand, studies done in Taipei[11], Finland[21] and Thailand [1] found that diabetes was not significantly associated with tuberculosis treatment outcome.

We were unable to analyze the relationship between multi drug resistance tuberculosis (MDR-TB) and the treatment outcome since there was only one case (0.2%) MDR-TB identified in the study. The small number makes the analysis inappropriate. This figure is almost equal with the country's proportion of MDR-TB (0.1%) since more than a decade ago[4]. This might indicate that MDR-TB is not yet a serious problem in Malaysia. However, underreporting or under-detection of such cases may also contribute to the small number.

There were 108 (23%) patients who did not have BCG scar. This finding contradicted with the Malaysian Ministry of Health report of excellent BCG coverage (>95%) since 1993[14]. Even though BCG vaccination was proved to give significant protection from tuberculosis [22], it was not associated with the treatment outcome as shown in the present study. Result from the present study also showed that tuberculin test, sputum smear and sputum culture were not predictors for the treatment outcomes. A delay in the diagnosis of tuberculosis increases the risk of poor clinical outcome including death and transmission of tuberculosis[23]. However, the study showed that duration of delay for diagnosis was not a significant predictor for the treatment outcome. This is probably due to poor categorization of the duration of delays as a result of limited secondary data available. In a future study, duration of delay should be categorized into two groups which are patient's delay (period between onset of the first symptom and the first visit to any health provider) and health system's delay (period between first visit to health provider and commencement of anti-TB treatment).

Among all the associated factors studied, only age, chest X-ray findings and HIV co-infection were found to be significant associated factors for the treatment outcomes. This is consistent with findings from previous studies in which older age will increase the risk for unfavorable treatment outcomes. A study by Anunnatsiri et al (2005) showed that age over 60 years was significantly associated with treatment interruption and treatment failure[1]. Another study by Talay et al (2007) stated that age more than 46 years was found to be a significant risk factor for non-successful treatment outcome[9]. The lowering of the immune system level with increasing age would be the reason for unsuccessful TB treatment.

Concerning chest X-ray findings, the study showed that patients with advanced lesions will have more than six times the risk to have unsuccessful treatment outcome compared to those who has minimal chest X-ray findings. This is in line with findings by Bao et al (2007) who found that treatment success outcome among patients with cavitations was 0.7 times (95% CI 0.53–0.91) less likely than among the patients without cavitations[10]. Similarly, another study by Talay et al (2007) showed that successful treatment outcome among patients with extensive lesions on chest X-rays was 0.5 (95% CI 0.2-1.3) times less likely than those with non-extensive lesions[9]. Extensive lesion on chest X-ray might represent some delay for diagnosis in seeking TB treatment and finally contribute to the unsuccessful TB treatment.

The rising incidence of TB due to the effect of HIV in both developed and developing countries is well recognized[24]. Infection with HIV has modified the epidemiology, pathogenesis and clinical manifestations of tuberculosis and is by far the most potent risk factor for tuberculosis; known for the progression of latent *Mycobacterium*

tuberculosis infection to active TB and for the rapid progression of new infection to TB[24]. Previous studies also proved that HIV was associated with TB treatment outcomes which include treatment interruption[1] and death[18]. In line with that, the present study significantly showed that the risk for having unsuccessful TB treatment outcome will increase by 23 times in patients with HIV positive compared to those non-HIV patients. However, the result showed that the confidence intervals are wide which might be due to small numbers was eligible for assessment. About 12% of all respondents were HIV positive, which shared almost the same prevalence of HIV in new TB cases in Malaysia (11%) as reported by WHO in 2006[7]. This finding stressed the need to enforce the Ministry of Health HIV/AIDS policy to include TB screening in all HIV positive individuals as being suggested by Zahiruddin and Naing[25]. The use of highly active antiretroviral therapy (HAART) during treatment for tuberculosis in HIV infected patients should also be considered as it has been shown to give a significant protection against mortality[26]. The use of HAART is also effective for preventing active TB and this effect is also additive when used with isoniazid[11]. However, further study is needed to obtain information about the risk for drug interactions and optimal time to initiate HAART in TB with HIV patients.

CONCLUSION

Advanced age, advanced chest X-ray findings and HIV co-infection were the relevant associated factors for unsuccessful tuberculosis treatment outcome. A large proportion of unsuccessfully treated cases could be identified at entry by screening for age, chest X-rays and HIV status and specially targeted measures could be taken. The use of DOTS (Directly Observed Treatment, Short-course) should be given more focus and priority among this high risk group of patients.

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